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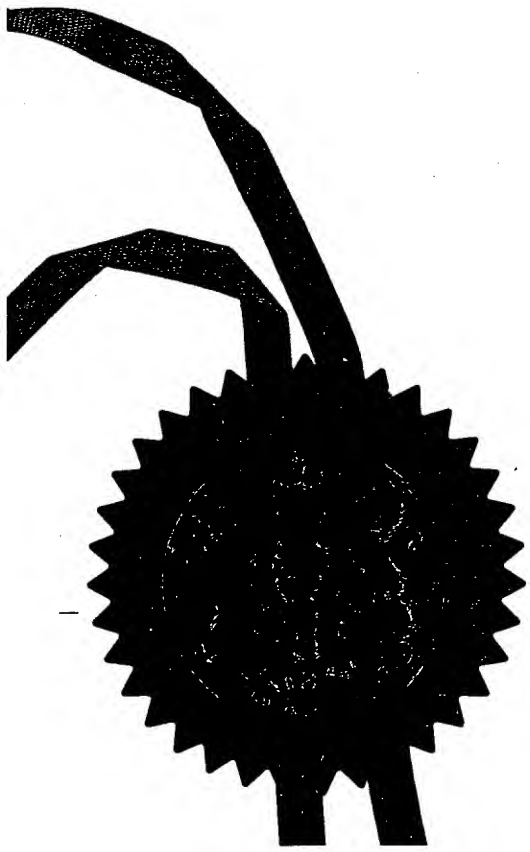

Signed W. Russell

Dated 10 AUG 1994

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-40CT 930002B8446 PAT 1 77 UC 25.00

Your reference 136420

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Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

The Patent Office — Request for grant of a Patent

Form 1/77

Patents Act 1977

❶ Title of invention

1 Please give the title of the invention

SYNTHESIS OF 17-(3-PYRIDYL) STEROIDS

❷ Applicant's details

❑ **First or only applicant**

❷ Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

2a If you are applying as a corporate body please give:

Corporate name: BRITISH TECHNOLOGY GROUP LTD

Country *(and State of incorporation, if appropriate)*: U.K.

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases**, please give the following details:

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LONDON

UK postcode *(if applicable)*: SE1 6BU

Country: U.K.

ADP number *(if known)*: 414001

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Yes [X] No [ ] ➡ ***go to 3b***

⬇ ***please give details below***

Agent's name MR. R.K. PERCY, M.A. C.P.A.,

Agent's address BRITISH TECHNOLOGY GROUP LTD
101 NEWINGTON CAUSEWAY
LONDON

Postcode SE1 6BU

Agent's ADP number 12 408335 07003n.

3b: *If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.*

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❹ Reference number

4 Agent's or applicant's reference number *(if applicable)* 136420

❺ Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ ***go to 6***

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❻ Declaration of priority

❻ If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

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- *any applicant is a corporate body.*

❼ Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes [ ] No [X] ➡ ***A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

❽ *Please supply duplicates of claim(s), abstract, description and drawing(s).*

❽ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)	3	Description	
Abstract	1	Drawing(s)	

8b Which of the following documents also accompanies the application

Please mark correct box(es)

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 – Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 – Preliminary Examination/Search	
Patents Form 10/77 – Request for Substantive Examination	

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❾ Request

I/We request the grant of a patent on the basis of this application.

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Signed R.K. PERCY Keith Percy
Agent for the Applicant

Date 29 SEPTEMBER 1993 *(day month year)*

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136420

SYNTHESIS OF 17-(3-PYRIDYL) STEROIDS

Background of the invention

1. Field of the invention

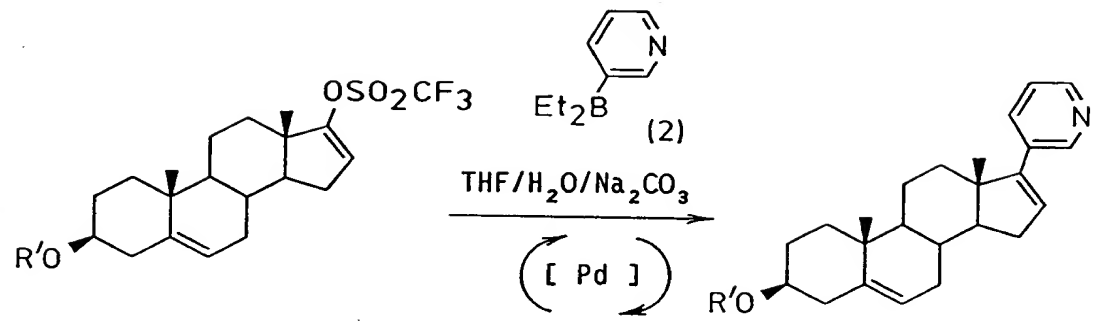
This invention relates to the synthesis of steroids which have a 16, 17-double bond and a 17-(3-pyridyl) substituent.

2. Description of the related art

In the unpublished patent applications GB 9305269.4 (British Technology Group Ltd.) and PCT GB93/00531 (British Technology Group Ltd., S.E. Barrie, M. Jarman and G.A. Potter), both filed on 15th March 1993, we have described 16,17-ene-17-(3-pyridyl) steroids as a class of compounds useful for treatment of androgen- and oestrogen- dependent disorders, especially prostatic and breast cancer respectively. A few of these compounds have previously been mentioned in the literature as intermediates in synthesis, to prepare final products having other uses, but otherwise these compounds were new. Since that date, posters have been presented, notably at the SmithKline Beecham Research Symposium, Robinson College Cambridge, England, 25-26 March 1993 and at the British Association for Cancer Research meeting in Sheffield, England, 28-31 March 1993. The Cambridge poster describes the synthesis of an exemplified 16,17-ene-17-(3-pyridyl) steroid as follows:

Synthesis of this molecule was envisaged via a possible palladium catalysed cross-coupling [G.A. Potter and R. McCague, J. Org Chem. 55, 6184-6187 (1990)] of a steroidal enol triflate (trifluoromethylsulfonate) with a suitable 3-pyridyl nucleophilic coupling partner. This was achieved by using diethyl(3-pyridyl)borane in aqueous THF, with sodium carbonate as nucleophilic activator. The reaction proceeded remarkably efficiently, without possible triflate hydrolysis or ethyl coupling, providing the desired compound in 80% isolated yield (Scheme 1):

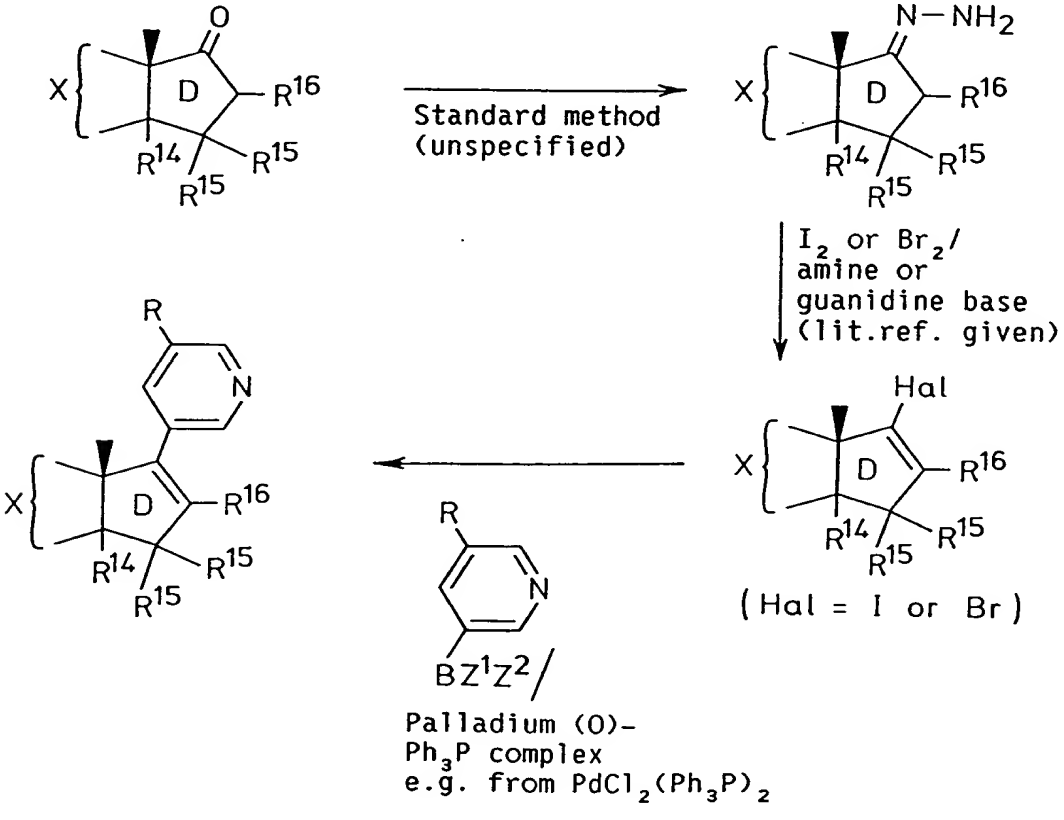
Scheme 1



(wherein in the final compound R' = H)

Triflates are expensive starting materials, so an alternative route is desirable. Further, notwithstanding what might appear from a literal reading of the poster, to obtain the 3-ol the reaction has to be carried out on the 3-acetate as protecting group, not the 3-ol. The 3-acetate is then hydrolysed to the 3-ol subsequently in a separate step. Our unpublished patent application proposes an alternative route, as follows (Scheme 2):

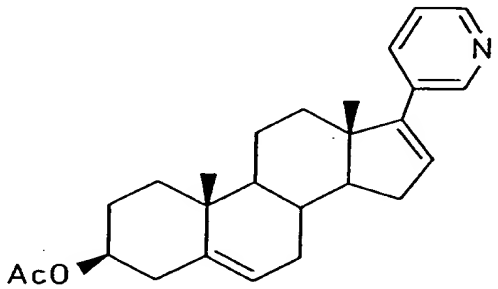
Scheme 2



wherein X represents the residue of the A, B and C rings of a steroid, R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms, R^{14} represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms and each of the R^{15} substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1-4 carbon atoms, a hydroxy group or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R^{14} and one of the R^{15} groups together represent a double bond and the other R^{15} group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms, and R^{16} represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms, and Z^1 and Z^2 independently represent hydroxy or alkoxy or alkyl of 1-4 carbon atoms each, preferably ethyl or methoxy.

Summary of the invention

It has now surprisingly been found that in the preparation of the preferred compound, 3β-acetoxy-17-(3-pyridyl)androsta-5, 16-diene, of formula (1):

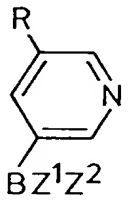


(1)

the reaction can be carried out via the vinyl iodide intermediate, but using the unprotected 3β-hydroxy compound, while keeping the proportion of organoboron compound (borane)

used in the cross-coupling reaction to not more than 1.2 equivalents per equivalent of steroid and that the reaction product can then be isolated without chromatography. This route is therefore amenable to large scale synthesis.

The principle of the invention may be expressed as a method of preparing a 3β-hydroxy- or 3β- (lower acyloxy) 16,17-ene-17-(3-pyridyl)-substituted steroid, wherein the 3β-(lower acyloxy) group of the steroid has from 2 to 4 carbon atoms, which comprises subjecting a 3β-hydroxy-16,17-ene-17-iodo or -bromo steroid to a palladium complex-catalysed cross-coupling reaction with a (3-pyridyl)-substituted borane, in which the pyridine ring is substituted at the 5-position by an alkyl group of 1 to 4 carbon atoms or is unsubstituted thereat, especially with a said borane of formula (2):



(2)

wherein R is a hydrogen atom or an alkyl group of 1-4 carbon atoms and Z^1 and Z^2 independently represent hydroxy or alkoxy or alkyl of 1-3 carbon atoms each or Z^1 and Z^2 together represent an alkylenedioxy group of 2 or 3 carbon atoms, in a proportion of from 1.0 to 1.2 equivalents of boron compound per equivalent of steroid, in an organic liquid, which is a solvent for the 3β-hydroxy steroidal reaction product, and optionally acylating the 3β-hydroxy reaction product.

Description of the preferred embodiments

Preferred embodiments of the invention include the features set forth in the claims, q.v.

Preferably the 17-iodo ("vinyl iodide") starting compound has a D-ring with optional substitution in position 14, 15 and/or 16 as shown in Scheme 2. Most preferably it is prepared from the corresponding 17-ketone, conveniently via the corresponding

hydrazone. Preferably the vinyl iodide is unsubstituted in the 14, 15 and 16-positions, in which case it can be prepared from dehydroepiandrosterone (DHEA). In the hydrazination it is preferable to use hydrazine hydrate together with a catalytic amount of a proton provider which is most preferably hydrazine sulfate.

The hydrazone is preferably iodinated with iodine or brominated with bromine in the presence of a strong base such as a tetraalkylguanidine, especially tetramethylguanidine which is cheaply and readily available.

In the cross-coupling reaction, the boron compound is preferably a diethylborane or a dimethoxyborane (Z^1=Z^2=Et or -OMe). Other boranes include those in which the boron atom is part of a cyclic ether ring e.g. as in Z^1,Z^2 = 1,2-ethylenedioxy or 1,3-propylenedioxy. The proportion of borane added is no more than 1.2 moles of boron per mole of steroid, preferably about 1.1. The palladium compound is a palladium (O) phosphine complex such as tetrakis(triphenylphosphine) palladium (O) or a compound reducible to a palladium (O) phosphine species, especially bis(triphenylphosphine) palladium (II) chloride.

The cross-coupling reaction is preferably carried out in two phases, one aqueous, one organic. The organic phase comprises an organic solvent for the 3β-hydroxy steroidal reaction product, especially tetrahydrofuran (THF). Other cyclic ethers such as dioxane could be used in place of THF. Preferably, a nucleophilic activator, such as sodium carbonate, is used in which case it is normally present in the aqueous phase. After the reaction, inorganic salts are removed by first adding another organic solvent, preferably diethyl ether, which is a solvent for the organoboron contaminants produced in the reaction product, and miscible with the first-mentioned organic solvent (e.g. THF), but immiscible with water, whereafter the organic, e.g. (THF-diethyl ether), phase and water (aqueous phase) can be separated. After this separation, the THF and diethyl ether are evaporated as a mixture and the remaining reaction product is

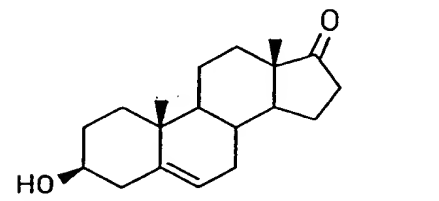
washed with a third organic solvent, which can be diethyl ether, preferably cooled to below room temperature, most especially to 10°C or lower. The 3β-hydroxy steroid reaction product has a low solubility in the ether, which, importantly, removes the organoboron compound/s (and also the palladium compound/s).

To prepare the 3β-acyloxy (alkylcarbonyloxy) compounds, standard acylating agents such as acetyl, propionyl or butyryl chloride or anhydride can be used. The method of acylation may require some modification for isolation of the product.

The following Example illustrates the invention.

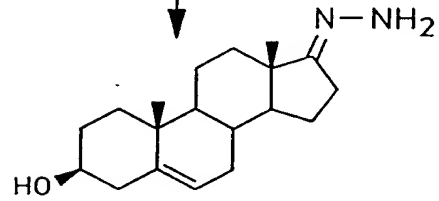
EXAMPLE

Illustrative reaction scheme



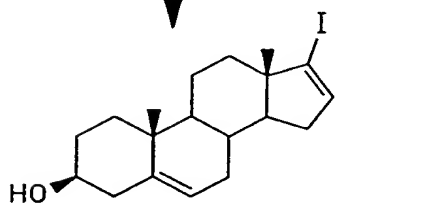
Dehydroepiandrosterone (DHEA)

(a) Modification of lit. methods B. Schweder et al. J. Prakt. Chem., 201-204, 335, (1993).



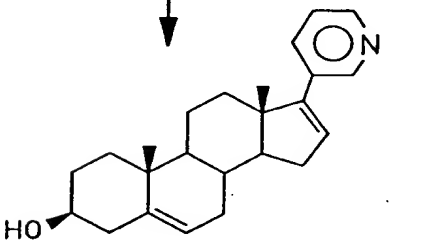
Hydrazone of DHEA

(b) Modification of lit methods D.H.R. Barton et al., Tet. Lett., 1605-1608, 24, (1983), Tetrahedron, 147-162, 44, (1988).



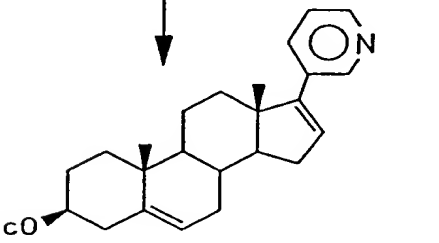
Steroidal vinyl iodide

(c) (Modification of methodology described in the earlier patent application).



3β-hydroxy steroidal reaction product

(d) Standard acetylation



3β-acetoxy steroidal reaction product

(a) Dehydroepiandrosterone-17-hydrazone

To a stirred solution of dehydroepiandrosterone (28.8g, 0.1 mol) in ethanol (500ml) was added hydrazine hydrate (19.5ml, 0.4 mol), followed by a solution of hydrazine sulfate (65mg, 0.5 mmol) in water (2ml). After stirring for 3 days the mixture was poured into water (3 litres) to precipitate the product as a white crystalline solid. The product was collected by filtration on a sinter, washed with cold water (2 x 50ml), then with Et_2O (50ml). The product was then dried in vacuo, firstly over silica gel, and finally over P_2O_5, to give the title compound as a white crystalline solid (29.6g, 98%).

Notes 1) The method of Schweder et al., p. 202, compound No. 2 therein (using triethylamine) gave a very fine crystalline product which was difficult to filter.

2) The method of Schweder et al. p. 203, compound No. 4 therein (using sodium acetate buffer) gave a slightly lower yield (96%) in trial experiments, whereas the modified procedure used above gives a product amenable for filtation, and in excellent yield (98%).

(b) 17-Iodo-androsta-5,16-dien-3β-ol

To a solution of iodine (53.3g, 0.21 mol) in THF (2l), cooled by an ice/water bath to 0°C was added 1,1,3,3-tetramethylguanidine (63 ml, 57.6g, 0.50 mol).

A solution of dehydroepiandrosterone-17-hydrazone (30.25g, 0.10 mol) in THF (750 ml) was then added slowly to the above iodine solution via a transfer needle over about 2h, whilst maintaining the reaction temperature at 0°C. After all the hydrazone solution was added, the mixture was filtered, and the filtrate concentrated. The remaining oil was then heated on an oil bath for 4h, allowed to cool, and dissolved in Et_2O. The Et_2O solution was washed with 1M HCl until the aqueous phase was acidic, washed with 0.5M NaOH, then 1M $Na_2S_2O_3$, and finally with water. The Et_2O phase was separated, dried ($MgSO_4$), and concentrated to give the crude product. Recrystallisation from Et_2O/hexane (3:2) afforded the title compound as off-white crystals (35.8g, 90%).

(c) 17-(3-Pyridyl)androsta-5,16-dien-3β-ol

Diethyl(3-pyridyl)borane (3.23g, 22 mmol) from Aldrich Chemical Co. Ltd. was added to a stirred solution of 17-iodo-androsta-5,16-dien-3β-ol (7.96g, 20 mmol) in THF (120ml) containing bis(triphenylphosphine)palladium (II) chloride (140mg, 0.2 mmol). An aqueous solution of sodium carbonate (2M, 50ml) was then added and the mixture heated, with stirring, by an oil bath at 80°C for 48h, and allowed to cool.

The mixture was partitioned between Et_2O and water the organic phase was separated, dried (Na_2CO_3) and twice concentrated from Et_2O by evaporation to remove THF (with Et_2O). The residual solid was then washed with Et_2O (100ml), the Et_2O solution decanted off, and the remaining white solid recrystallised from toluene (3.94g, 56%).

Notes 1) The time required for completion needs to be made longer than when using the vinyl triflate (48h vs 1h) since it has been found that the vinyl iodide reacts much more slowly.

2) It has been found that a smaller excess of borane than described in the earlier application (for the vinyl triflate) aids in isolation of product.

3) The work-up procedure enables the product to be isolated without chromatography, thereby enabling scaling up.

(d) 3β-Acetoxy-17-(3-pyridyl)androsta-5,16-diene

To a stirred suspension of finely powdered 17-(3-pyridyl)androsta-5,16-dien-3β-ol (3.50g, 10 mmol) in dry diethyl ether (150ml) containing triethylamine (2.3ml, 16 mmol) and dimethylaminopyridine (0.012g, 0.1 mmol) was added acetyl chloride (1.0ml, 14 mmol). The mixture was then stirred at ambient temperature for 12h, over which time a thick white precipitate of triethylammonium chloride had formed. The mixture was then filtered and the filtrate concentrated to afford the crude product which was recrystallised firstly from ethanol/water (1:1), then finally from hexane to afford the title compound (3.30g, 84%).

Notes 1) This is a modification of standard acetylation conditions [e.g. acetic anhydride or acetyl chloride with pyridine base and dimethylaminopyridine catalyst, see e.g. J. Wicha and M. Masnyk, Bulltein of the Polish Academy of Sciences: Chemistry 33 (1-2), 19-27 (1985)] which uses diethyl ether as solvent with acetyl chloride and triethylamine base so that the by-product triethylammonium chloride, which is insoluble in diethyl ether, is precipitated as it forms in the reaction. The reaction mixture can thus be filtered to remove the precipitated by-product, and evaporation of the filtrate provides the acetylated material.

2) It is essential that the final product, rather than the vinyl iodide or a precursor thereof, is acetylated.

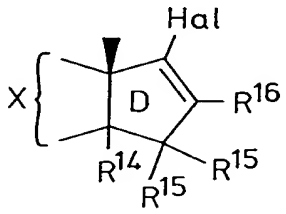
The following claims define some important aspects of the invention, but do not purport to include every conceivable aspect for which protection might be sought in subsequent continuing and foreign patent applications, and should not be construed as detracting from the generality of the inventive concepts hereinbefore described.

CLAIMS

1. A method of preparing a 3β-hydroxy- or 3β- (lower acyloxy) 16,17-ene-17-(3-pyridyl)-substituted steroid, wherein the 3β-(lower acyloxy) group of the steroid has from 2 to 4 carbon atoms, which comprises subjecting a 3β-hydroxy-16,17-ene-17-iodo or -bromo steroid to a palladium complex-catalysed cross-coupling reaction with a (3-pyridyl)-substituted borane in which the pyridine ring is substituted at the 5-position by an alkyl group of 1 to 4 carbon atoms or is unsubstituted thereat, in a proportion of from 1.0 to 1.2 equivalents of borane per equivalent of steroid, in an organic liquid, which is a solvent for the 3β-hydroxy steroidal reaction product and, where the 3β-(lower acyloxy) group is to be prepared, reacting the resulting 3β-hydroxy steroidal reaction product with an acylating agent effective to replace the hydroxy group by a said lower acyloxy group.

2. A method according to claim 1, wherein the 3β-hydroxy steroidal reaction product is reacted with an acetylating agent to give the corresponding 3β-acetoxy-16,17-ene-17-(3-pyridyl) steroid.

3. A method according to claim 1 or 2 wherein the starting steroid has a D-ring of the following partial formula

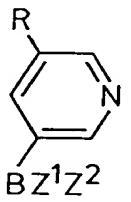


wherein Hal is I or Br, X represents the residue of the A, B and C rings of the steroid, R^{14} represents the residue of the A, B and C rings of a steroid, R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms, R^{14} represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms and each of the R^{15} substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1-4 carbon atoms, a hydroxy group

or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R^{14} and one of the R^{15} groups together represent a double bond and the other R^{15} group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms, and R^{16} represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms.

4. A method according to claim 3 wherein the starting steroid is 3β-hydroxyandrost-5-en-17-one dehydroepiandrosterone).

5. A method according to any preceding claim wherein the (3-pyridyl)-substituted borane is of formula:



wherein R is a hydrogen atom or an alkyl group of 1-4 carbon atoms and Z^1 and Z^2 independently represent hydroxy or alkoxy or alkyl of 1-3 carbon atoms each or Z^1 and Z^2 together represent an alkylenedioxy group of 2 or 3 carbon atoms.

6. A method according to any preceding claim wherein the proportion of the borane is about 1.1 equivalent.

7. A method according to any preceding claim in which the reaction is carried out in two phases, one of which is aqueous and the other of which comprises the said organic liquid.

8. A method according to claim 7 wherein the organic liquid is a first organic liquid, the reaction product-containing mixture is worked up by adding a second organic liquid, which is miscible with the first, but immiscible with water, separating the organic and aqueous phases, evaporating the mixture of organic solvents and washing the residue in a third organic liquid under conditions in which the organoboron contaminants are more soluble than the 3β-hydroxy steroidal reaction product.

9. A method according to claim 8 wherein the first organic liquid comprises tetrahydrofuran and the second and third organic liquids comprise diethyl ether.

10. A method according to claim 9 wherein the residue is washed with the third organic liquid cooled to below room temperature.

ABSTRACT

SYNTHESIS OF 17-(3-PYRIDYL) STEROIDS

A method of preparing a 3β-hydroxy- or 3β- (lower acyloxy) 16,17-ene-17-(3-pyridyl)-substituted steroid, wherein the 3β-(lower acyloxy) group of the steroid has from 2 to 4 carbon atoms, which comprises subjecting a 3β-hydroxy-16,17-ene-17-iodo or -bromo steroid to a palladium complex-catalysed cross-coupling reaction with a (3-pyridyl)-substituted borane in which the pyridine ring is substituted at the 5-position by an alkyl group of 1 to 4 carbon atoms or is unsubstituted thereat, in a proportion of from 1.0 to 1.2 equivalents of borane per equivalent of steroid, in an organic liquid, which is a solvent for the 3β-hydroxy steroidal reaction product and, where the 3β-(lower acyloxy) group is to be prepared, reacting the resulting 3β-hydroxy steroidal reaction product with an acylating agent effective to replace the hydroxy group by a said lower acyloxy group.